CHAPTER SEVENTEEN

MALARIA

1.0 Overview of Malaria

Malaria is a parasitic infectious disease presenting with fever, chills and profuse sweating. However, patient with malaria infection may be completely asymptomatic.

Diagnosis

The clinical features of malaria vary from mild to severe. The disease presentation will vary according to patient's state of immunity, the intensity of the infection and the presence of accompany conditions such as malnutrition, anaemia and other diseases.

Signs and Symptoms inludes:-

malaise, fever, fatigue, muscle pain, nausea, anorexia, chill, rigors, sweats, headache, cough, vomiting and diarrhea etc.

The above signs and symptoms are not specific for malaria and can be found in other disease conditions. Therefore it is necessary to investigate for other causes of febrile illness.

Laboratory investigation is mandatory and urgent for all patients admitted with severe malaria. Parasite-based diagnosis by microscopy is important while rapid diagnostic tests (RDTs) may be an alternative. Laboratory tests should be interpreted in conjunction with clinical findings.

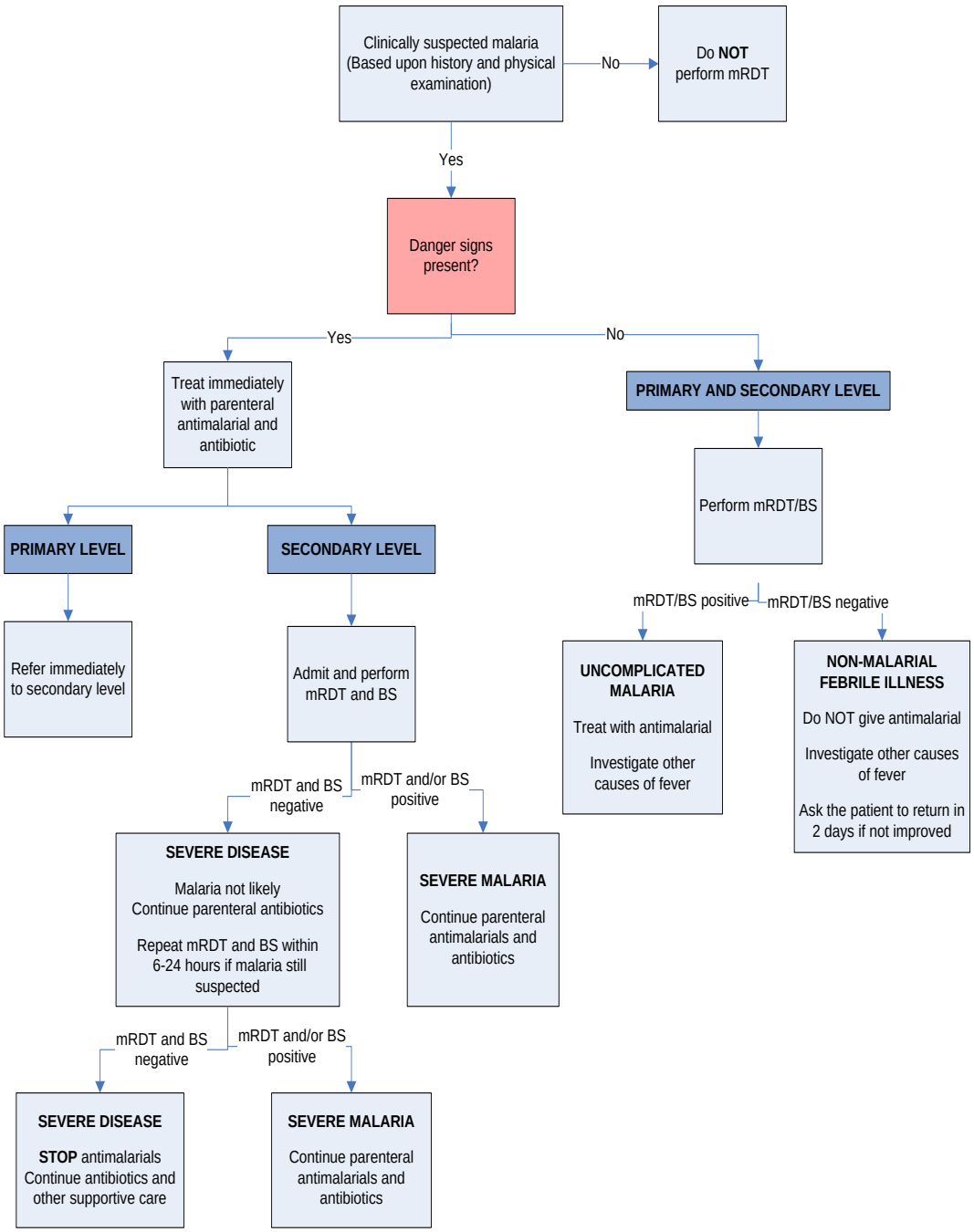
Management

The management and referral for patient with malaria will be determined by the clinical presentation and the diagnosis of either uncomplicated or severe disease, as well as results of RDT and/or microscopy (see flow chart -Figure 1).

In children under five years of age, IMCI practical algorithms for management of sick child with fever should be used to ensure full assessment and appropriate case management of children, in particular at the primary level health.

In the case of negative blood slide/RDT without signs or symptoms of severe disease, look for other causes, manage and follow up accordingly, and ask the patient to come back if condition does not improve. The exception is in children under 5 years living in high malaria transmission areas, if unable to return for follow up or in case the condition worsens, treat as for uncomplicated malaria.

Figure1: Management of suspected malaria based on both clinical presentation and laboratory investigations



2.0 Treatment of Uncomplicated Malaria

Definition: Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

Give antimalarial medicines only to those who test positive for parasites.
Treatment on the basis of clinical suspicion alone should only be considered if parasitological diagnosis is not accessible.

The objectives of treatment of uncomplicated malaria are:
- To provide rapid and long lasting clinical and parasitological cure
- To reduce morbidity including malaria related anaemia
- To halt the progression of simple disease into severe and potentially fatal disease

Since the progression towards severe and fatal disease is rapid, especially in children under five years of age, it is recommended that diagnosis and initiation of treatment of uncomplicated malaria should be within 24 hours from the onset of symptoms.

First line:

Artemether Lumefantrine (ALu).

- Standard tablet: fixed formulation Artemether 20mg, Lumefantrine 120mg
- Dispersible tablet: fixed formulation for children, Artemether 20 mg, Lumefantrine 120mg

Dosage regimen

Table 1: Dosage of Artemether 20mg & Lumefantrine 120mg (ALu) tablets

		Day 1		Day 2		Day 3		
	Dose	1st	2nd	3rd	4th	5th	6th	Colour Code
	Hours	0 (*)	8	24	36	48	60	
Kg	Age	tablets	tablets	tablets	tablets	tablets	tablets	
up to 15	0 to 3 years	1	1	1	1	1	1	Yellow
15 up to 25	3 years up to 8 years	2	2	2	2	2	**2**	**Blue**
25 up to 35	8 years up to 12 years	3	3	3	3	3	**3**	**Red**
35 and above	12 years and above	4	4	4	4	4	**4**	**Green**

The first dose should be given as direct observed treatment (DOT); the second dose should strictly be given after 8 hours; subsequent doses could be given twice daily (morning-evening) in the second and third day of treatment until completion of 6 doses.

Note: Artemether-Lumefantrine is not recommended for:

- **Infants below 5kg body weight:**

Malaria is quite uncommon in infants below 2 months of age (approximately below 5 kg). Rarely, congenital and neonatal malaria does occur. ALu is currently not recommended for infant below 5kg body weight because the dosing and safety profile of the partner component lumefantrine is not well studied. Therefore, an artemisinin alone is the drug of choice as 1st line treatment in the category of neonates and infants below 5Kg, treating as for severe malaria. Injectable quinine remains a suitable alternative where artesunate is not available. See section on Treatment of Severe Malaria for dosage of parenteral artesunate.

- **First trimester of pregnancy:** See section on Malaria in pregnancy

During the second and third trimesters of pregnancy Artemether-Lumefantrine should be used as drug of choice for treatment of uncomplicated malaria

As far as possible malaria cases should be followed up on the third day if symptoms persist or immediately if the condition worsens. Failure to respond to the recommended drug regimen indicates the need for further investigations and appropriate management, with referral if needed.

Where a patient returns between 4 to 14 days after treatment with ALU complaining of continued symptoms of malaria, non-response should be considered and the following recommendations followed after a full history and examination:

- Where laboratory facilities are not available and malaria is still suspected, second line treatment should be started immediately with strict follow up
- Where laboratory facilities are available, a blood smear (and not RDT) should be examined. If parasites are found second line treatment should be started and treatment failure recorded. If parasites are not found other causes for the symptoms should be sought and treated accordingly

Second line for uncomplicated malaria:
Dihydroartemisinin plus Piperaquine (DPQ)

- Fixed-dose combination with tablets containing

C: Dihydroartemisinin (D) and Piperaquine (PQ).
40 g D + 320 mg PQ
20 mg D + 160 mg PQ

Dosage regimen

Table 2: Dosage of DPQ for defined categories by body weight

Body Weight (kg)	Daily dose (mg)		Tablet strength and number of tablets per dose
	Piperaquine	Dihydroartemisinin	
5 to <7	80	10	½ x 160mg / 20mg tablet
7 to <13	160	20	1 x 160mg / 20mg tablet
13 to <24	320	40	1 x 320mg / 40mg tablet
24 to <36	640	80	2 x 320mg / 40mg tablets
36 to <75	960	120	3 x 320mg / 40mg tablets
75 to 100	1,280	160	4 x 320mg / 40mg tablets

Based on 4 mg/kg/day Dihydroartemisinin and 18 mg/kg/day Piperaquine once a day for 3 days

3.0 Treatment of Severe Malaria

Severe *Plasmodium falciparum* malaria is a medical emergency. Delay in diagnosis and provision of appropriate treatment may lead to serious complications and even death. In Tanzania the commonest presentations of severe malaria are severe anaemia and coma (cerebral Malaria). Complications include hyperpyrexia, convulsions, shock, hypoglycaemia, metabolic acidosis, acute renal failure or pulmonary oedema

Early diagnosis of severe malaria based upon a complete history, physical examination and where possible, blood smear or rapid diagnostic test (RDT) examination for malaria parasites. Taking and reporting of blood smear must not be allowed to delay treatment unduly.

Definition: In a patient with P.falciparum asexual parasitaemia and no other obvious cause of symptoms the presence of one or more of features listed below classify the patient as suffering from severe malaria.

Table 3: Features of severe malaria

Clinical features	Description/criteria
Prostration/extreme weakness	Unable to stand or sit up without support
Impaired consciousness	Altered level of consciousness Acute confusional state, coma
Change of behaviour	Hallucinations, delusions, agitation
Convulsions	Repetitive abnormal muscular movements
Respiratory distress (due to lactic acidosis and/or pulmonary oedema)	Acidotic breathing: deep and laboured breathing Pulmonary oedema: laboured breathing, restlessness, blood stained frothy sputum especially in adults
Bleeding tendency/DIC	Easy/prolonged bleeding
Jaundice	Yellow colouration of mucus membranes
Circulatory collapse/shock	Low systolic BP and fast pulse rate
Vomiting everything	Throwing up after every feed/drink
Inability to drink or breast feed	Not able to swallow

NOTE: If effective management of severe malaria and supportive care for complications is not possible, patients should be given pre-referral treatment and referred immediately to an appropriate facility for continued treatment.

Pre-referral treatment options:

B: Artesunate IM/rectal

OR

B: Quinine IM

Rectal artesunate is the recommended pre-referral treatment at the community level. At a health facility the pre-referral dose of parenteral therapy should be initiated without delay.

Pre-referral rectal artesunate:

- Available as suppository containing 50mg or 100mg or 400mg

Dosage regimen:

Single dose of 10 mg/kg body weight artesunate should be administered rectally. In the event that an artesunate suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and, especially in young children, the buttocks should be held together for 10 min to ensure retention of the rectal dose of artesunate.

Table 4: Dosage for initial (pre-referral) treatment using rectal artesunate

Weight (Kg)	**Age**	**Artesunate dose (mg)**	**Regimen (single dose)**
5-8.9	0-12 months	50	One 50 mg suppository
9-19	13-42 months	100	One 100 mg suppository
20-29	43-60 months	200	Two 100 mg suppository
30-39	5-13 years	300	Three 100 mg suppository
40-59	>14 years	400	One 400 mg suppository
60-80	>14 years	800	Two 400 mg suppository
>80	>14 years	1200	Three 400 mg suppository

Pre-referral artesunate IM:

- Artesunate is provided as a powder vial of artesunic acid with a 1ml ampoule of diluent sodium bicarbonate solution 5%. Reconstitute for IM injection:
    - The vial of artesunatepowder is mixed with 1ml of diluent sodium bicarbonate solution to form sodium artesunate. Shake for 2-3 minutes until completely dissolved and solution is clear. The solution is 60mg/ml artesunate
    - Dilute with **2m**l of 5% dextrose or dextrose/saline. The concentration is now 20mg/ml artesunate.

  One vial makes 3ml solution (20mg/ml) for **IM** injection. Use immediately; discard any solution not used within 1 hour.

Dosage regimen:

Single dose of 2.4 mg/kg body weight administered by intramuscular injection to the anterior thigh after reconstituted and diluted as directed.

Table 5: Dosage for initial (pre-referral) treatment using artesunate IM (20mg/ml solution)

Weight (Kg)	Age	Artesunate dose in ml (Solution 20mg/ml)
<5	0-xx months	0.5 ml
5-8	xx-xx months	1 ml
9-12	xx-xx months	1.5 ml
13-16	xx-xx months	2 ml
17-20	xx-xx months	2.5 ml
21-25	xx-xx months	3 ml
26-29	xx-60 months	3.5 ml
30-33	5-xx years	4 ml
34-37	x-xx years	4.5 ml
38-41	x-xx years	5 ml
42-45	>14 years	5.5 ml
46-50	>14 years	6 ml
51-54	>14 years	6.5 ml
55-58	>14 years	7 ml
59-62	>14 years	7.5 ml
63-66	>14 years	8 ml
67-70	>14 years	8.5 ml
71-75	>14 years	9 ml
76-79	>14 years	9.5 ml
80-83	>14 years	10 ml
84-87	>14 years	10.5 ml
88-91	>14 years	11 ml
92-95	>14 years	11.5 ml
96-100	>14 years	12 ml

Pre-referral Quinine IM:

- Dilution of Quinine Dihydrochloride injection (300 mg/ml) for intra-muscular use:

One part of Quinine solution should be diluted with four parts water for injection to a concentration of 60 mg/ml. This dilution will minimize the risk of sterile abscess formation.

Dosage regimen:

Give single dose of 10mg of quinine salt per kg bodyweight (not exceeding a maximum dose of 600mg). The calculated dose should be divided into two halves and then administered by deep intra-muscular injection preferably into the mid anterolateral aspect of the thigh (one injection on each side).

Table 6: Dosage for initial (pre-referral) treatment using intramuscular quinine (IM)

Age (years)	Weight (Kg)	Volume of undiluted Quinine (300 mg/ml)	Volume of diluents (to add to each dose)	Total volume of diluted Quinine (60 mg/ml)
2 up to 4 months	4 up to 6	0.2 ml	0.8 ml	1.0 ml
4 up to 9 months	6 up to 8	0.3 ml	1.2 ml	1.5 ml
9 up to 12 months	8 up to 10	0.4 ml	1.6 ml	2.0 ml
12 months up to 3yrs	10 up to 14	0.5 ml	2.0 ml	2.5 ml
3 up to 5	15 up to 19	0.6 ml	2.4 ml	3.0 ml
5 up to 8	19 up to 25	0.7 ml	2.8 ml	3.5 ml
8 up to 12	25 up to 35	1.0 ml	4.0 ml	5.0 ml
12 up to 14	35 up to 50	1.4 ml	5.6 ml	7.0 ml
14 up to 16	50 up to 60	1.8 ml	7.2 ml	9.0 ml
16 and above	60 and above	2.0 ml	8.0 ml	10.0 ml

Refer with clinical summary to the nearest hospital when clinical need dictates (e.g. blood transfusion or intensive care)

Treatment of Severe Malaria

Treatment in both children and adults where facilities for admission and effective management of severe malaria are available:

First choice:

Artesunate 2.4 mg/kg body weight IV or IM given on admission (time = 0), then at 12 hours and 24 hours, then once a day.

Artesunate (i.v. infusion)

- Artesunate is provided as a powder vial of artesunic acid with a 1ml ampoule of diluent sodium bicarbonate solution 5%. Reconstitute for **IV** injection:
    - The vial of artesunatepowder is mixed with 1ml of diluent sodium bicarbonate solution to form sodium artesunate. Shake for 2-3 minutes until completely dissolved and solution is clear. The solution is 60mg/ml artesunate
    - Dilute with **5m**l of 5% dextrose or dextrose/saline. The concentration is now **10mg/ml** artesunate.

  One vial makes 6ml solution (10mg/ml) for **IV** injection. Use immediately; discard any solution not used within 1 hour.

Table 7: Dosage for treatment using intravenous artesunate (IV; 10mg/ml solution)

Weight (Kg)	Age	Artesunate dose in ml (Solution 10mg/ml)
<5	0-xx months	1 ml
5-8	xx-xx months	2 ml
9-12	xx-xx months	3 ml
13-16	xx-xx months	4 ml
17-20	xx-xx months	5 ml
21-25	xx-xx months	6 ml
26-29	xx-60 months	7 ml
30-33	5-xx years	8 ml
34-37	x-xx years	9 ml
38-41	x-xx years	10 ml
42-45	>14 years	11 ml
46-50	>14 years	12 ml
51-54	>14 years	13 ml
55-58	>14 years	14 ml
59-62	>14 years	15 ml
63-66	>14 years	16 ml
67-70	>14 years	17 ml
71-75	>14 years	18 ml
76-79	>14 years	19 ml
80-83	>14 years	20 ml
84-87	>14 years	21 ml
88-91	>14 years	22 ml
92-95	>14 years	23 ml
96-100	>14 years	24 ml

Alternative if parenteral artesunate is not available:

Quinine 20 mg salt/kg body weight (BW) on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 hours; infusion rate should not exceed 5 mg salt/kg BW per hour.

Quinine (i.v. infusion)

Quinine dose: 10 mg/kg body weight of salt, to be diluted in 5-10 ml/kg body weight of 5% Dextrose or dextrose-saline and infused over 4 hours and repeated every 8 hours. Infusions should be discontinued as soon as the patient is able to take oral medication. Patients should be properly instructed to complete the 7-day treatment with quinine tablets or, alternatively, a full course of ALu may be administered to complete treatment

The **drop rate** for quinine IV infusion is calculated as follows:

Drop rate per minute = amount of fluid to be infused (in ml) x 20 (drop factor) / time period to be infused (in minutes)

The table below is given for easier calculation.

Table 8: Dilution schedule and drop rate for intravenous Quinine administration

Age (years)	Weight(kg)	Quinine dose	Volume of undiluted quinine solution (300mg/ml)	Amount of fluid to be infused (in 4 hours)	Drop rate per minute
2 up to 4 months	4 up to 6	60 mg	0.2 ml	50 ml	4 drops
4 up to 9 months	6 up to 8	90 mg	0.3 ml	100 ml	8 drops
9 up to 12months	8 up to 10	120 mg	0.4 ml	100 ml	8 drops
12 up to 3yrs	10 up to 14	150 mg	0.5 ml	100 ml	8 drops
3 up to 5	15 up to 19	180 mg	0.6 ml	150 ml	13 drops
5 up to 8	19 up to 25	210 mg	0.7 ml	200 ml	17 drops
8 up to 12	25 up to 36	300 mg	1.0 ml	250 ml	21 drops
12 up to 14	36 up to 50	420 mg	1.4 ml	350 ml	30 drops
14 up to 16	50 up to 60	540 mg	1.8 ml	500 ml	42 drops
16 and above	60 and above	600 mg	2.0 ml	500 ml	42 drops

Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, complete treatment by giving a complete course (3 days) of:

A: Artemether plus lumefantrine (ALu),

OR

C: Dihydroartemisinin plus piperaquine (DPQ),

General measures for severe malaria

• Treatment of hypoglycaemia. Hypoglycaemia remains a major problem in the management of severe malaria especially in young children and pregnant women. It should be deliberately looked for and treated accordingly.

• **Coma** (cerebral malaria): maintain airway, nurse on side, and exclude other causes of coma (e.g. hypoglycaemia, bacteria meningitis); avoid giving corticosteroids
• **Hyperpyrexia:** fanning, paracetamol (preferred over NSAIDs)
• **Convulsions:** maintain airways; treat with rectal or IV diazepam.
• **Hypoglycaemia:** urgent and repeated blood glucose screening;
• In children: give 5 mls/kg of 10% dextrose OR 2.5 mls/kg of 25% dextrose as bolus; if 50% dextrose solution is available, it should be diluted to make 25% by adding an equal volume of water for injection or normal saline
• In adults: give 125 mls of 10% dextrose OR 50 mls of 25% dextrose dextrose as bolus
• Where dextrose is not available, sugar water should be prepared by mixing 20 gm of sugar (4-level tea spoons) with 200 ml of clean water. 50 ml of this solution is given ORALLY or by naso-gastric tube if unconscious
• **Severe anaemia**: transfusion of packed cells if Hb equal or less than 4 g/dl and/or signs of heart failure and/or signs of respiratory distress
• **Acute pulmonary oedema:** Prop patient up to 45 degree angle; review fluid balance and run patient on "dry side"; give diuretic but avoiding inadequate perfusion of kidneys; set up Central Venous pressure (CVP) line, give oxygen. Intubation/ventilation may be necessary
• **Acute renal failure:** exclude pre-renal causes, check fluid balance and urinary sodium. If

adequately hydrated (CVP>5cm) try diuretics. Haemodialysis /haemofiltration (or if available peritoneal dialysis) should be started early in established renal failure.

4.0 Management of malaria in pregnancy

Malaria is an important cause of morbidity and mortality for the pregnant woman, the foetus and the newborn. The effects of malaria in pregnancy are related to the malaria endemicity, with abortion more common in areas of low endemicity and intrauterine growth retardation more common in areas of high endemicity. Early diagnosis and effective case management of malaria illness in pregnant women is crucial in preventing the progression of uncomplicated malaria to severe disease and death.

4.1 Management of uncomplicated malaria in the first trimester

If a laboratory blood slide is negative, it does not rule out malaria. RDTs have an added value, as they can be positive even if parasites are hidden in the placenta.

Note: During the second and third trimesters of pregnancy Artemether-Lumefantrine is the drug of choice for treatment of uncomplicated malaria

First trimester:
During the first trimester of pregnancy, treat with quinine plus clindamycin for seven days or quinine alone if clindamycin is not available or unaffordable.

Quinine is safe in pregnancy. In therapeutic doses it does not induce labour. Uterine contractions and foetal distress with the use of quinine may be attributable to fever and effects of malaria disease. Clindamycin is considered safe in the first trimester of pregnancy. At present, artemisinin derivatives cannot be recommended in the first trimester of pregnancy. However, they should not be withheld if treatment is considered life saving for the mother, and other suitable antimalarials are not available. For dosage of quinine, see section on treatment of severe malaria.

S: Clindamycin dosage: 10mg/Kg (O) twice daily for 7 days.

Note: Lactating women should receive the recommended antimalarial treatment (including ALu)

4.2 Management of severe malaria in pregnancy

Pregnant women infected with malaria are more susceptible to develop severe malaria.
They commonly present with one or more of the following signs/symptoms: high fever, hyperparasitemia, low blood sugar, severe haemolytic anaemia, cerebral malaria, pulmonary oedema.

The management of severe malaria in pregnant women does not differ from the management of severe malaria in other adult patients, except pregnant women in the first trimester. (See section on Treatment of Severe Malaria).

The risk of quinine induced hypoglycaemia is greater in pregnant than non-pregnant women. Blood sugar should be monitored regularly and if falls below 2.5 mmol/L (< 45
mg/dl) give IV 10% or 25% dextrose. While the patient is on IV Quinine treatment, pay particular attention to the feeding of the patient.

4.3 Intermittent preventive treatment in pregnancy (IPTp)

The drug of choice for IPTp is **Sulfadoxine/Pyrimethamine (SP).** SP remains the drug of choice for IPTp even though it is no longer the first line drug for malaria treatment. This is because the aim of IPTp is to prevent the worst effects of infection, rather than to cure a potentially life threatening illness. As such, lower efficacy antimalaria is acceptable for IPTp than for curative purposes. It is particularly important that drugs used in pregnancy are known to be safe. It is also likely that drugs with a long half-life are the most effective when used as IPTp.

The first IPTp dose is administered between 20-24 weeks of gestational age. The second IPTp dose should be administered at 28 – 32 weeks.

NOTE:

- IPTp should be administered as direct observed treatment (DOT) during an antenatal care visit
- Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.